REMARKS

Claims 1-20 are pending and have been rejected. Minor editorial amendments have been made to claims 1, 2, 3, 9, and 13-18. Claims 19 and 20 have been canceled. Claims 21-23 have been added, based on the specification, for example, at page 25, lines 20-23. Claims 24-27 have been added, based on the specification, for example, at page 15, lines 14-17 and 28-31. Claims 28 and 29 have been added, based on the specification, for example, at page 21, line 30 to page 22, line 14. Claims 1-18 and 21-29 remain in the case.

Claims 1-20 stand rejected under the second paragraph of Section 112. The claims have been amended to address the points raised by the examiner.

Claims 19 and 20 are rejected under Section 102(b) or, in the alternative, under Section 103(a) over any of Chen *et al.*, *Blood* 88: 1052 (Aug. 1996), Shen *et al.*, *Blood* 89: 3354 (May 1997), and Zhang *et al.*, translation of *Chinese J. Hematology* (Feb. 1996), volume 17. Claims 19 and 20 have been canceled.

Claims 1-20 are rejected under Section 103(a) based on the combined teachings of Shimotsuura *et al.*, Shen *et al.*, Chen *et al.*, Zhu *et al.*, Sun *et al.*, and Zhang *et al.*

All of the cited documents disclose the treatment of acute promyelocytic leukemia (APL) with either (1) arsenic trioxide, or (2) a composition which contains arsenic stone and HgCl, along with other ingredients. Shimotosuura *et al.* report on studies on the antineoplastic action of arsenic trioxide in a mouse model. Shen *et al.* discloses the use of arsenic trioxide in the treatment of 15 relapsed patients with APL. Chen *et al.* discloses *in vitro* studies in NB_4 cells, leading to a discussion of possible cellular and molecular mechanisms of arsenic trioxide in the treatment of APL. Zhu *et al.* discloses arsenic-induced PML targeting onto nuclear bodies. Sun *et al.* discloses treatment of 32 cases of APL, denoted acute early granulocytic leukemia in the translation. Zhang *et al.* discloses the treatment of 72 cases of APL.

None of the cited documents makes any disclosure that would lead the skilled artisan to use an arsenic compound to treat cancers other than APL, such as

(1) a solid tumor, as claimed in claim 1,

(2) metastatic neoplastic disease, as claimed in claim 2,

(3) melanoma, breast, colon, ovarian, renal, central nervous system, bladder, prostate or lung cancer, as claimed in claim 3, and

(4) a hematopoietic disorder other than APL, selected from the group consisting of acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, myeloid metaplasia, myeloid metaplasia, myeloid dysplastic syndrome, multiple myeloma and plasmocytoma.

In the first instance, positive results in treating APL would not have led a skilled artisan to predict similar results when treating such diverse cancers as solid tumors, metastatic neoplastic disease, or any of the cancers listed in (3) above. Nor would such results have suggested the use of an arsenic compound in the treatment of the other hematopoietic disorders listed in (4) above.

Indeed, the art as a whole, including several of the cited documents, contains teachings that would have led a skilled artisan to conclude that an arsenic compound would not be effective in treating these different categories of neoplasia. Rather, the art taught that arsenites are highly toxic compounds which actually could ***cause*** cancer. Because of this toxicity and the ability to cause cancer, arsenic compounds had been discarded as potential anti-cancer drugs.

For example, when used in animals, high concentrations of inorganic arsenic given by intraperitoneal (IP) injection caused damage to target enzymes and marked toxicity. In fact, the experimental results in mice that are reported starting on page 10 of Shimotosuura *et al.* actually show a minimal improvement in survival, at best, and in many instances a actual ***decrease*** in life span for most of the arsenic trioxide compositions and concentrations administered.

More specifically, when arsenic trioxide 5 mg/kg was given by IP injection, there was only a 10.4% improvement in survival as compared to untreated mice (Table 1). This minimal improvement in survival is insignificant, and arsenic trioxide was considered to be an inactive drug according to the criteria for new cancer drugs outlined by the World Health Organization, which requires a greater than 25% improvement in survival before a

drug is considered to be "effective." Indeed, more favorable results in increasing life span were generated in Shimotosuura when arsenic trioxide was administered in combination with an arsenic ***antidote***, such as 2,3-dimercapto-1-propane-sulfonic acid (DMPS) or meso-2,3-dimercaptonecinic acid (DMSA), suggesting that the arsenic compounds did not improve survival rates in the mice. Moreover, the mouse model used in Shimotosuura *et al.* is not considered by those of ordinary skill in this art to be predictive of efficacy in humans. Thus, both the lack of predictability of the mouse model and the actual results achieved with that model in Shimotosuura *et al.* are factors which would have led a skilled artisan to discount the value of arsenic compounds in the treatment of neoplasias as presently claimed.

In this same vein, Sun *et al.* suggests that arsenic must be used in combination with arsenic antidotes, and with other toxic agents, in order to achieve positive results. Sun *et al.* used Ai-Ling No. 1, a combination of arsenic stone or arsenic sublimate and HgCl. See paragraph 9 of the Rule 132 declaration of Guo-Qiang Chen that was submitted in SN 08/702,011 (copy appended). The arsenic and mercury compounds were administered "in combination with the Chinese medical practice of administering the treatment according to the pattern." This entails the co-administration of numerous other ingredients to counteract the effects of the arsenic, including Ginseng and Astragalus Four Agents Decoction, Ginseng White Tiger Decoction and Bone-Clearing Powder, Antelope Horn and Forsythia Toxin-Resolving Decoction, Heart-Draining Decoction or Gentian Liver-Draining Decoction, Construction-Clearing Decoction, and Bone-Clearing Powder and Pulse-Engendering Powder. This teaching would not have led a skilled artisan to conclude that it was an arsenic compound that led to the positive results reported.

Even those documents which do suggest that arsenic trioxide is the active ingredient in achieving positive results in the treatment of APL would not have led a skilled artisan to the conclusion that an arsenic compound might have positive effects in treating ***other*** neoplasias. For example, Zhu *et al.* disclose that APL is associated with the t(15:17) translocation, which generates a PML/RARα fusion protein between PML, a growth suppressor localized on nuclear matrix-associated bodies and RARα, a nuclear receptor for retinoic acid (RA). Based on their results, Zhu *et al.* conclude that in APL cells, arsenic targets PML and PML/RARα onto nuclear bodies (NB) and induces their degradation.

Similarly, Chen *et al.* posit that arsenic trioxide induces NB_4 cell apoptosis with down-regulation of Bcl-2 expression and modulation of PML proteins. The art thus identifies a particular mechanism, ***specific to APL and APL cells***, by which arsenic exerts its effects. In light of this specific mode of action, a skilled artisan would not have predicted that arsenic compounds would have been effective in treating the other neoplasias as recited in applicants' claims.

Despite these teachings in the art, Examiner Pak urges that, "while the references do not expressly disclose the treatment of practically all cancer types, as claimed, one having ordinary skill in the art would have been motivated to utilize arsenic compounds such as arsenic trioxide to treat solid tumors and other neoplastic diseases as claimed herein because arsenic compounds have been taught to possess antineoplastic properties, in addition to having been clinically demonstrated as being effective in treating leukemia." This broad-brush approach contrasts sharply with the examiner's treatment of an earlier application, U.S. serial No. 08/702,011, which applicants make of record in an information disclosure statement filed herewith, and which, at one time, included claims to treating "cancer" with arsenic trioxide. (The '011 application embodies the results of two publications cited by the examiner, Shen *et al.* and Chen *et al.*) In relation to the "cancer treatment" claims of the '011 application, Mr. Pak argued that enablement was lacking because "broad cancer treatment is claimed when only one type of cancer is shown to be treated...however, in the field of treating cancer, no one substance has been found that successfully treat[s] all types of cancer." Thus, the examiner discounted the predictive value of a showing for one cancer type, relative to the efficacy of arsenic trioxide, but now exalts the predictive value of the same showing!

In any event, the prior art in question illuminates a very specific mechanism for the effect of arsenic on APL. Given so narrow a teaching, one of ordinary skill would not "have been motivated to use arsenic compounds such as arsenic trioxide" (in the examiner's words) to treat cancers other than APL. In contrast, applicants have shown positive results, wholly unexpected, against a wide variety of cell lines in the National Cancer Institute tumor cell line-screening system. These results in the specification clearly show that an arsenic compound was effective in inhibiting growth in cell lines of many common forms of cancer. This is very significant in view of the high correlation between drug anti-tumor

activity in the NCI system and subsequent clinical effect in patients. Indeed, this screening approach identified taxol as applicable to a variety of cancers, and subsequent clinical results validated the broad anti-cancer activity of taxol.

Finally, the combined teachings of the cited documents would not have led a skilled artisan to combine another therapeutic agent with an arsenic compound in the treatment of neoplastic diseases as claimed in claim 13, and particularly with a chemotherapeutic or radiotherapeutic agent, as claimed claim 14. There is no suggestion that any benefit might accrue to combinations with other therapeutic agents, particularly with chemotherapeutic or radiotherapeutic agents as recited in claim 14, or the specific therapeutic agents recited in claim 16.

In view of the foregoing amendments and remarks, it is believed that all claims are in condition for allowance. Reconsideration of all rejections and a notice of allowance are respectfully requested. Should there be any questions regarding this application, the examiner is invited to contact the undersigned attorney at the phone number listed below.

Respectfully submitted,

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MARKED-UP VERSIONS OF AMENDED CLAIMS

1. (Amended) A method of [treating] treatment of solid tumors in a [mammal] human in need of such treatment, which comprises administering a therapeutically effective amount of one or more arsenic compounds to said [mammal] human.

2. (Amended) A method of [treating] treatment of metastatic neoplastic disease in a [mammal] human in need of such treatment, which comprises administering a therapeutically effective amount of one or more arsenic compounds to [a mammal in need of such therapy] said human.

3. (Amended) A method of [treating] treatment of melanoma, breast, colon, ovarian, renal, central nervous system, bladder, prostate or lung cancer in a human in need of such treatment, which comprises administering a therapeutically effective amount of one or more arsenic compounds to said human.

9. (Amended) The method of claim 4 wherein said tumor of the central nervous system is selected from the group consisting of neuroblastoma, retinoblastoma, glioblastoma [or] and oligodentroglioma.

13. (Amended) A method for [treating] treatment of neoplastic diseases in a human in need of such treatment, which comprises administering to [a] said human an effective amount of an arsenic compound, or a pharmaceutically acceptable salt thereof, in combination with an effective amount of at least one other therapeutic agent.

14. (Amended) The method of claim [12] 13 in which said other therapeutic agent is a chemotherapeutic agent or radiotherapeutic agent.

15. (Amended) The method of claims 1, 2, 3, or [12] 13 in which said administration is made parenterally, topically, dermally, directly into the tumor or orally.

16. (Amended) The method of claim [12] 13 in which said other therapeutic agent is selected from the group consisting of etoposide, cisplatin, carboplatin, estramustine phosphate, vinblastine, methotrexate, hydroxyurea, cyclophosphamide, doxorubicin, 5-fluorouracil, taxol, diethylstilbestrol, VM-26 (vumon), BCNU, all-trans retinoic, acid, procarbazine, cytokines, and therapeutic vaccines[, and other immunomodulators].

17. (Amended) The method of claim 1, 2, 3 or [12] 13 in which said administration is made via an implantation device.

18. (Amended) A method of [treating] treatment of hematopoietic disorders in a [mammal] human in need of such treatment, which comprises administering one or more arsenic compounds to said [mammal] human, wherein said hematopoietic disorder is selected from the group consisting of acute lymphocytic leukemia, chronic lymphocytic leukemia, hairy cell leukemia, myeloid metaplasia, myeloid dysplastic syndrome, multiple myeloma and plasmacytoma.